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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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RICHARD ARON OSMAN
SCIENCE AND TECHNOLOGY LAW GROUP
75 DENISE DRIVE
HILLSBOROUGH, CA 94010

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/649,859	BERG, RICHARD A.	
	Examin r	Art Unit	
	Michael Wilson	1632	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence encoding human procollagen operably linked to a promoter that functions in mammary glands, a fertilized mammalian egg or a mouse ES cell comprising a nucleic acid sequence encoding human collagen operably linked to a promoter that functions in mammary glands, a non-human mammal whose genome comprises a nucleic acid sequence encoding human collagen operably linked to a promoter that functions in mammary glands, wherein said mammal secretes human collagen into its milk and a method of preparing human collagen comprising recovering milk for said transgenic non-human mammal, and recovering human collagen from the recovered milk, does not reasonably provide enablement for any fertilized non-human egg or embryonic stem cell as broadly claimed or for a mammal further modified to contain an expression system that effect the production of post-translational

modification enzymes for procollagen as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable any fertilized non-human egg having the construct claimed (claim 4). The construct is used to produce proteins in the milk of transgenic mammals. However, the eggs claimed encompass any non-human animal. Non-mammalian animals do not have mammary glands. The specification does not teach how to use non-mammalian eggs having a construct with a mammary-gland specific promoter. As such, it would require one of skill undue experimentation to determine how to use non-mammalian fertilized eggs having a construct that expresses proteins in mammary glands.

The specification does not enable any non-human ES cells as broadly claimed (claim 5). Krimpenfort taught making transgenic bovines expressing proteins in their milk using fertilized oocytes displaying germline transmission of transgenes (1991, Bio/Technology, Vol. 9, pg 844-847). Krimpenfort did not use bovine ES cells. In fact, Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught that ES cells providing germline transmission were only available in mice (pg S38, col. 1, para. 1). Therefore, the art at the time of filing and the specification does not teach how to make ES cells that provide germline transmission other than mouse ES cells. The specification does not correlate methods of isolating mouse ES cells that provide germline transmission to other methods of isolating other species of ES cells that provide germline transmission. Given what was known in the art taken with the teachings in the specification, it

would have required one of skill undue experimentation to obtain a non-human ES cell other than a mouse ES cell.

The specification does not enable a transgenic non-human mammal merely comprising the expression system as claimed (claim 6). The expression system must be passed through the germline (see Krimpenfort, pg 844, col. 1, para. 1) which requires that the construct is part of the genome of the mammal for protein expression to occur. The art at the time of filing did not teach how to obtain protein expression in milk without the construct being a part of the genome. As such, the claims should be limited to non-human mammals whose genomes comprise the construct.

In addition, claim 6 is not enabled as broadly claimed because it does not recite the phenotype of the non-human mammal. The specification does not provide an enabled use for a transgenic comprising the construct that does not produce procollagen or collagen in its milk. As written, the claims do not clearly set forth that protein is expressed in the milk. A positive, clear statement indicating the phenotype of the mammal would overcome this rejection.

The specification does not enable a mammal having a second construct that effects production of post-translational modification enzymes for procollagen as claimed (claim 7). The art at the time of filing was that the phenotype of transgenic mice was unpredictable because of the variability of transgene expression (Mullins above; pg S37, col. 2, line 7). In addition, Wall (1996, Theriogenology, Vol. 45, pages 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice

(page 62, line 7). The specification contemplates using such constructs in combination with constructs encoding procollagen (pg 16, line 8; pg 17, line 6; pg 18, line 1). In particular, the specification describes methods of producing both constructs in the same animal by putting both constructs in at the same time or by producing two separate transgenic animals that are bred to combine the constructs (pg 19, line 16 through pg 21, line 7). The guidance provided in the specification is inadequate to overcome the unpredictability in the art. The specification states expression of both of the enzymes must occur together because the enzymes function together as a tetrameric protein (pg 21, line 1). The specification does not teach the expression of any enzymes in the milk of transgenic mammals. The specification does not provide adequate guidance such that the expression of both enzymes is the same, that the enzymes are capable of forming a tetrameric protein or that the amount of tetrameric protein obtained is capable of post-translational processing of procollagen. In addition, the α-subunit of prolyl hydorxylase has not yet been completely described or sequenced (pg 10, line 3, of the specification). Without such guidance, taken with the unpredictability in the art for one of skill to obtain a phenotype of interest, it would have required one of skill undue experimentation to obtain the mammal claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 7 are indefinite because the use of "containing" is confusing. Containing is closed language. Therefore, a mammal having been modified "to contain" an expression system (claim 1, line 4; claim 4, line 1; claim 5, line 2; claim 7, line 2) contains only the expression system. However, the mammal does not contain just an expression system.

Claim 1 is indefinite because the phrase "coding nucleotide sequence encoding at least one human procollagen operably linked to control nucleotide sequences that effect expression specifically in milk protein-secreting epithelial cells of said mammary glands under conditions wherein said coding nucleotide sequence is expressed to secrete human procollagen..." is unclear. It is unclear if the control sequences cause expression of procollagen or merely "effect" some other protein. It is unclear if "specifically" means "exclusively" or "mostly". It is unclear if procollagen expression occurs in the milk because it is unclear whether the "conditions" as claimed actually occur. The claim does not clearly set forth the description of the regulatory element or the step of obtaining protein expression or secretion in the milk.

Claim 1 is indefinite because the steps of the claim are not in a logical order. The step of recovering milk should be after obtaining secretion of the protein in the milk and before recovering protein from the milk.

Claims 1 and 2 are indefinite because the use of the word "coding" to describe a nucleotide sequence encoding a protein is redundant.

Claim 3 is indefinite because "the pro-α1 chain" lacks antecedent basis. It is unclear if a pro-α1 chain of collagen is a subunit of procollagen or if it is procollagen. Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418) refers to Pro-α2(I) collagen as a type of collagen. However, as written, it is not clear that the "chain" is procollagen.

Claim 7 is indefinite because it does not clearly set forth the structure or function of the expression system. The claim does not require that the system encodes an enzyme; it only has to "effect" the production of enzymes. The claim does not require that the enzyme function occurs or that procollagen is cleaved to form collagen. As such, the claim as written is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buhler (Feb. 1990, Biotechnol., Vol. 8, pg 140-143) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379).

Buhler taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter for producing the protein in the milk of transgenics (pg 143, col. 2, "Construction..."). Buhler taught fertilized eggs comprising a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter (pg 143, col. 2, "Construction..."). The fertilized eggs were transplanted into pseudopregnant females and transgenics comprising the transgene were obtained ("Generation..."). The protein was expressed and secreted in the mammary gland of the transgenics and isolated from the milk (pg 141, col. 1, "Tissue specific transcription..."). The fertilized eggs of Buhler become blastocysts which inherently comprise ES cells as claimed because the fertilized eggs were 19.5 hours post-fertilization at which time ES cells occur ("Generation..., line 2). Buhler did not teach the construct encoded procollagen. However, Khillan taught a construct for expressing the pro-α1 chain of Type I collagen in transgenics.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the β-casein promoter as taught by Buhler wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillan. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Buhler with the pro-α1 chain of Type I collagen to produce the pro-α1 chain of Type I collagen in the milk of transgenics. One of ordinary skill in the art at the time the invention was made would have recognized that the transgenic described by Buhler was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary

skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland of the transgenic to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining pro-α1 chain of Type I collagen expression in mammary glands because Buhler obtained exogenous protein secretion in the mammary glands of transgenics and because Khillan obtained human pro-α1 chain of Type I production in transgenics. The combined teachings of Buhler and Khillan are no less than the specification which merely suggests making animals using methods known in the art and using the pro-α1 chain of Type I collagen (pg 13, line 26).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

4. Claims 1, 2 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buhler (Feb. 1990, Biotechnol., Vol. 8, pg 140-143) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418).

Buhler taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter for producing the protein in the milk of transgenics (pg 143, col. 2, "Construction..."). Buhler taught fertilized eggs comprising a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter (pg 143, col. 2, "Construction..."). The fertilized eggs were transplanted into pseudopregnant females and transgenics comprising the transgene were obtained ("Generation..."). The protein was expressed

and secreted in the mammary gland of the transgenics and isolated from the milk (pg 141, col. 1, "Tissue specific transcription..."). The fertilized eggs of Buhler become blastocysts which inherently comprise ES cells as claimed because the fertilized eggs were 19.5 hours post-fertilization at which time ES cells occur ("Generation..., line 2). Buhler did not teach the construct encoded procollagen.

However, Lee taught a construct for expressing human Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the β-casein promoter as taught by Buhler wherein the protein was Pro-α2(I) collagen as taught by Lee. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Buhler with the Pro-α2(I) collagen of Lee to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the rabbit described by Buhler was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human Pro-α2(I) collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression and secretion in mammary glands because Buhler obtained exogenous protein

from the milk of the rabbits and because Lee obtained Pro-α2(I) expression in cells that do not normally produce collagen. The combined teachings of Buhler and Lee are no less than the specification which suggests making animals using methods known in the art and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

5. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379).

Krimpenfort taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 845, Fig. 1). The construct was injected into fertilized eggs (pg 845, col. 2, line 18). The fertilized eggs were transplanted into pseudopregnant female bovines and transgenic offspring were obtained (pg 8846, col. 1, "DNA analysis"). The fertilized eggs comprise ES cells as claimed because the fertilized eggs were injected with the construct between 18-23 hours after fertilization which divides and inherently produce ES cells within the embryo. Krimpenfort does not expressly teach obtaining protein expression in the mammary gland or isolating the protein from the milk; however, claim 6 does not require the transgenics secrete protein in their mammary gland. It is noted that Krimpenfort taught the purpose of obtaining the transgenics was to express the protein in their mammary gland

(pg 844, col. 2, line 7-10). Krimpenfort did not teach the construct encoded procollagen or the transgenic bovine comprised a construct encoding procollagen.

However, Khillan taught a construct encoding the human pro-α1 chain of Type I collagen, transfecting liver cells with the construct and obtaining functional expression of the pro-α1 chain of Type I collagen in transgenic mice.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Krimpenfort wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillan. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Krimpenfort with the pro-α1 chain of Type I collagen taught by Khillian to produce the pro-α1 chain of Type I collagen in a bioreactor. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Krimpenfort was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Krimpenfort obtained exogenous protein expression in mammary glands of transgenics and because Khillan obtained pro-α1 chain expression in transgenics. The combined teachings of Krimpenfort and Khillan are no less than

the specification which suggests making animals using the method of Krimpenfort (pg 10, line 19) and using the pro-α1 chain of Type I collagen.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

6. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418).

Krimpenfort taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 845, Fig. 1). The construct was injected into fertilized eggs (pg 845, col. 2, line 18). The fertilized eggs were transplanted into pseudopregnant female bovines and offspring comprising the transgene were obtained (pg 8846, col. 1, "DNA analysis"). The fertilized eggs inherently comprise ES cells as claimed because the fertilized eggs were injected with the construct between 18-23 hours after fertilization which divides to produce ES cells within the embryo. The claim does not require obtaining expression in the mammary gland (see 112/2nd); however, Krimpenfort teaches the purpose of obtaining the offspring was to express the protein in their mammary gland (pg 844, col. 2, line 7-10). Krimpenfort did not teach construct comprised procollagen or the transgenic bovine comprised a construct encoding procollagen.

However, Lee taught a construct for expressing Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Krimpenfort wherein the protein was Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Krimpenfort with the Pro-α2(I) collagen to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Krimpenfort was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Krimpenfort obtained exogenous protein expression in mammary glands and because Lee obtained Pro-α2(I) expression in cells that do not normally produce collagen. The combined teachings of Krimpenfort and Lee are no less than the specification which suggests making animals using the method of Krimpenfort (pg 10, line 19) and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

7. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379).

Rein taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 39, Fig. 1). The construct was injected into mouse ES cells which were transplanted into pseudopregnant females and transgenic offspring were obtained (sentence bridging pg 39-40). Claim 6 does not require obtaining expression in the mammary gland (see 112/2nd); however, Rein taught obtaining expression of the protein in their mammary gland and isolating the protein from the milk (pg 40, col. 2, line 5-8). Rein did not teach the construct comprised procollagen.

However, Khillan taught a construct encoding the human pro-α1 chain of Type I collagen, transfecting liver cells with the construct and obtaining functional expression of the pro-α1 chain of Type I collagen in transgenic mice.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Rein wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillian. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Rein with the pro-α1 chain of Type I collagen taught

by Khillian to produce the pro-α1 chain of Type I collagen in a bioreactor. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Rein was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Rein isolated exogenous human protein from the milk of transgenic mice and because Khillan obtained human procollagen expression in transgenic mice. The combined teachings of Rein and Khillan are no less than the specification which suggests making animals using methods known in the art and using the pro-α1 chain of Type I collagen.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

8. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strijker (1992, Conference Proceedings Series, Harnessing biotechnologoy for the 21st century, Ladisch ed., Publisher: American Chem. Soc. Marketing Division, pg 38-41) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418).

Strijker taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 39, Fig. 1). The construct was injected into mouse ES cells which were transplanted into pseudopregnant females and transgenic

offspring were obtained (sentence bridging pg 39-40). Claim 6 does not require obtaining expression in the mammary gland (see 112/2nd); however, Strijker taught obtaining expression of the protein in their mammary gland (pg 844, col. 2, line 7-10). Strijker did not teach the construct comprised procollagen.

However, Lee taught a construct for expressing human Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Strijker wherein the protein was Pro-α2(I) collagen as taught by Lee. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Strijker with the Pro-α2(I) collagen to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Strijker was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Strijker obtained exogenous human protein expression in mammary glands and because Lee obtained Pro-α2(I) expression in cells that do not normally

produce collagen. The combined teachings of Strijker and Lee are no less than the specification which suggests making animals using methods known in the art and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 2 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,111,165. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 requires obtain milk from a transgenic mammal as in claim 1 of '165. The constructs of claim 2 is used in the method of claim 1 in '165.

10. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,111,165 in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379). The claims of '165 are directed toward a method of making milk using a transgenic animal made with a construct encoding procollagen operably linked to a mammary gland promoter. '165 does not claim the procollagen was pro-α1 chain of type I collagen or an ES cell or fertilized egg comprising the construct. However, at the time of filing Khillan taught making transgenic mice encoding the pro-α1 chain of type I collagen. The mouse was made by transfecting ES cells with the construct. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic animal expressing procollagen in their milk as claimed in '165, wherein the procollagen was the pro-α1 chain of type I collagen and the animal was a mouse as taught by Khillan. One of ordinary skill in the art would have been motivated to transfect mouse ES cells to make a transgenic mouse because '165 claims making a mouse. One of ordinary skill in the art would have been motivated to make the pro-α1 chain of Type I collagen in milk to isolate the protein for purification.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

11. Claims 1, 2 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,895,833. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of making protein in claim 1 of '833 requires isolating the protein from milk as in claim 1 of the instant application. The construct used in each is the same and the protein produced is the same.

12. Claims 1, 2 and 4-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,895,833 in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379). The claims of '833 are directed toward a transgenic animal made with a construct encoding procollagen operably linked to a mammary gland promoter as well as a method of making procollagen using the transgenic animal. '833 does not claim the procollagen was a pro-α1 chain of type I collagen or an ES cell or fertilized egg comprising the construct. However, at the time of filing Khillan taught making transgenic mice encoding the pro-α1 chain of type I collagen. The mouse was made by transfecting ES cells with the construct. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic animal expressing procollagen in their milk as claimed in '833, wherein the procollagen was the pro-α1 chain of type I collagen and the animal was a mouse as tuaght by Khillan. One of ordinary skill in the art would have been

motivated to transfect mouse ES cells to make a transgenic mouse because '833 claims making a mouse. One of ordinary skill in the art would have been motivated to make the pro-α1 chain of Type I collagen in milk to isolate the protein for purification.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

13. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,962,648. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method used to make the product in '648 is the method of claim 1 which requires the construct and transgenic mammal of claim 2, 3 and 6.

14. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,667,839. Although the conflicting claims are not identical, they are not patentably distinct from each other because the transgenic mouse used to make the milk product in '839 is the transgenic animal of claim 6 and requires the construct of claim 2 in the instant application.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER